CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-788

CORRESPONDENCE

Robert E. Silverman, M.D., Ph.D.
Director
Regulatory Affairs

ORIGINAL

NEW DRUG APPLICATION

West Point PA 19486
Fax 610 397 2516
Tel 610 [illegible]
215 652 5000

MERCK
Research Laboratories

December 20, 1996

Jonathan K. Wilkin, M.D., Director
Division of Topical Drug Products
HFD-540, Room 17B-45
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Wilkin:

Original New Drug Application

NDA 20-788: Tablets PROPECIA™ (Finasteride)

Pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations, we are submitting a New Drug Application for finasteride tablets.

PROPECIA™, also referred to as finasteride, MK-906 and L-652,931, is a synthetic 4-azasteroid compound that is a specific inhibitor of Type II 5α-reductase, an intracellular enzyme which metabolizes the androgen testosterone into dihydrotestosterone (DHT). The drug has no affinity for the androgen receptor and does not act as an antiandrogen, nor does it have androgenic, estrogenic, antiestrogenic, progestational, or other steroidal properties. Therefore, a rationale exists for the use of finasteride in any disease where DHT is implicated in the development of target organ pathophysiology, and in which a reduction in DHT would be expected to interrupt the disease process. Male subjects born with a genetic deficiency of Type II 5α-reductase do not develop male pattern hair loss (androgenetic alopecia) or benign prostatic hyperplasia (BPH). These findings, coupled with a wealth of scientific investigation of the pathophysiology of androgen-mediated disorders, has led to the identification of DHT as the predominant androgen involved in the pathophysiological changes that occur in scalp and prostate with age.

Finasteride was originally developed for shrinkage of an enlarged prostate gland and is the subject of NDA 20-180, PROSCAR™ (finasteride tablets 5 mg), which was submitted April 15, 1991 and approved June 19, 1992 for the treatment of men with BPH.

PROPECIA™ is indicated for the treatment of men with male pattern hair loss (androgenetic alopecia) to increase hair growth and prevent further hair loss. The recommended dosage is one 1 mg daily.

The data summarized in this marketing application demonstrate that in men with male pattern hair loss, treatment with finasteride significantly increases hair growth and prevents further hair loss. This has been demonstrated with four different endpoints including both objective and subjective measures, replicated in two large Phase III pivotal studies. Clinically significant improvements are observed regardless of severity of hair loss, age, duration of hair loss, family history of baldness, or race. Finasteride has a highly selective mechanism of action and is effective at a low dose. It is well tolerated and is associated with very few adverse experiences.

Finasteride drug substance will be manufactured by Merck & Co., Inc., One Merck Drive, P.O. Box 100, Whitehouse Station, NJ 08889-0100 utilizing the facilities located at one or more of the Merck Manufacturing Division sites located at Ballydine, Kilsheelan Clonmel, County Tipperary, Ireland and Ponders End Enfield, Middlesex, UK. as defined in NDA 20-180.

Manufacturing, release testing, stability testing, and packaging of finasteride tablets, 1 mg will be conducted at the Merck Manufacturing Division (MMD) Arecibo, PR facility located at Merck Manufacturing Division, Division of Merck and Co., Inc., Road #2, Kilometer 60.3, Bo. Sabana Hoyos, Arecibo, PR 00688 and Merck Sharp & Dohme, Quimica de Puerto Rico, P.O. Box 6060, Barceloneta, PR 00617. Reference is made to agreements on a schedule for the submission of additional market container stability data from batches produced at both the research and manufacturing sites that were reached during telephone conferences between MRL and Agency representatives (Dr. DeCamp and Dr. Hathaway) on June 5 and December 17, 1996.

On November 28, 1994, Merck Research Laboratories held an End-of-Phase II meeting with FDA during which the proposed nonclinical and clinical programs designed to support the planned NDA were presented. On April 29, 1996, a pre-NDA meeting was held between MRL and FDA representatives to discuss the presentation and analysis of data in the NDA. The understandings and agreements reached at both of these meetings have been incorporated into this application.

This application is formatted as required in Title 21, paragraph 314.50 of the Code of Federal Regulations. It consists of a complete "archival" copy (Blue Binders), comprising 62 volumes and six "review" copies as described in the Statement of Organization which is attached to this letter. This NDA is being provided in electronic format and hard copy with the exception of Items 11 and 12 (case report tabulation and forms). Items 11 and 12 are being provided in electronic format only, for which a formal waiver from the requirements of 21 CFR 314.50(f) has been requested in accordance with current CDER policy. The electronic format of this submission will be submitted on or about January 15, 1997. MRL will contact the FDA to arrange an orientation to the electronic submission for all relevant Agency reviewers.

In accordance with the Prescription Drug User Fee Act of 1992, a check (Check Nos. : the User Fee I.D. No. is in the amount of , was sent to the Mellon Bank, Three Mellon Bank Center, 27th Floor (FDA 360909), Pittsburgh, PA 15259-0001, on December 17, 1996.

Pursuant to 21 CFR 314.50(k)(3), a complete field copy of the Chemistry, Manufacturing and Controls technical section (Item 3) has been submitted to the FDA Philadelphia District Office

(Attention: Ms. Debra L. Pagano). This field copy is a true copy of Item 3 as contained in the archival copy and review copies of this application.

Merck affirms that all sites listed in this application to support the manufacturing, packaging and labeling of PROPECIA™ for the market are available for pre-approval inspection at the time of this submission.

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc. did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

As provided for in 21 CFR 312.102, MRL would like to meet with the FDA approximately 90 days following receipt of this application. The purpose of this meeting will be to discuss the general progress and status of the review of this application and to determine if there are any important deficiencies identified at that time. MRL will contact the FDA to arrange for this meeting.

We consider the filing of this New Drug Application to be a confidential matter and request that the Food and Drug Administration not make its existence public without first obtaining written permission from Merck & Co., Inc.

Questions concerning this information should be directed to Robert E. Silverman, M.D., Ph.D. (610/397-2944) or, in my absence, Bonnie J. Goldman, M.D. (610/397-2383).

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Director, Regulatory Affairs

Attachment
Federal Express #1

Desk Copy: (Item 3) Philadelphia District Office, Attn.: Ms. Debra L. Pagano
U.S. Custom House Room 900, 2nd & Chestnut Streets
Philadelphia, PA 19106-2973
Federal Express #2

Desk Copy (Letter and Patent Information Only):
Mr. George Scott
Room 218 Chapman Building
1901 Chapman Avenue
Rockville, MD 20852
Hand Delivered

q/macs/lu/396

November 1, 1996

PROPECIA®
NDA 20-788
Finasteride

Item 13

Pursuant to the provisions of Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act 21 U.S.C. § 355 (b)(1), attached hereto please find the patent information for the above-identified application.

The undersigned declares that U.S. Patent Nos. 4,377,584, 4,760,071, 5,547,957 and 5,571,817 cover the formulation, composition, and/or method of use of PROPECIA® (finasteride 1 mg tablet). This product is currently being reviewed under Section 505 of the Federal Food, Drug and Cosmetic Act in the above-identified New Drug Application (NDA).

U.S. Patent No. 4,377,584, having an expiration date of March 22, 2000, claims a genus of chemical compounds including finasteride. This patent is owned by Merck & Co., Inc., Rahway, NJ.

The undersigned declares that U.S. Patent No. 4,377,584 covers the composition PROPECIA®. This product is the subject of this application for which approval is being sought.

U.S. Patent 4,760,071 has an expiration date of June 19, 2006 as extended by granted Patent Term Restoration under 35 U.S.C. § 156. This patent claims the chemical compound finasteride 17β-(N-tert-butyl-carbamoyl)-4-aza-5α-androst-1-ene-3-one. It is owned by Merck & Co., Inc., Rahway, NJ.

The undersigned declares that U.S. Patent No. 4,760,071 covers the composition PROPECIA®. This product is the subject of this application for which approval is being sought.

U.S. Patent No. 5,547,957, having an expiration date of October 15, 2013, claims a method of treating male pattern baldness with finasteride, 17β-(N-tert-butyl-carbamoyl)-4-aza-5α-androst-1-ene-3-one, at a dosage amount from

November 1, 1996

mg/day at least until the growth of at least one hair can be detected. This patent is owned by Merck & Co., Inc., Rahway, NJ.

The undersigned declares that U.S. Patent No. 5,547,957 covers the method of using PROPECIA®, the subject of this application for which approval is being sought.

U.S. Patent No. 5,571,817, having an expiration date of November 5, 2013, claims a method of treating androgenic alopecia with oral administration of finasteride, 17β-(N-tert-butyl-carbamoyl)-4-aza-5α-androst-1-ene-3-one. This patent is owned by Merck & Co., Inc., Rahway, NJ.

The undersigned declares that U.S. Patent No. 5,571,817 covers the method of using PROPECIA®, the subject of this application for which approval is being sought.

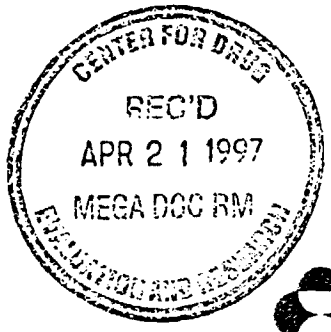
A claim of infringement could be asserted if a person not licensed by the owner of U.S. Patent Nos., 4,377,584, 4,760,071, 5,547,957, or 5,571,817 engaged in the manufacture, use or sale of PROPECIA®.

Sincerely,

Catherine D. Fitch
Senior Patent Attorney

/agb

Robert E. Silverman, M.D., Ph.D.
Director
Regulatory Affairs



Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

April 18, 1997 AMENDMENT

MERCK
Research Laboratories

Jonathan Wilkin, M.D., Director
Division of Dermatological Drug Products
HFD-540, Room N-214
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

ORIGINAL

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

NDA 20-788: PROPECIA™
(Finasteride)

SAFETY UPDATE REPORT

Reference is made to the above New Drug Application (NDA) submitted on December 20, 1997. Submitted with this letter is the Safety Update Report (SUR) for this NDA.

This SUR provides updated safety information for finasteride subsequent to the original NDA submitted on December 20, 1996. The SUR report period is defined as the time period between the individual study cutoff dates established for the original NDA through November 26, 1996, and extends the safety profile for approximately 6 months. This SUR provides new clinical and laboratory safety data for a total of 1740 patients with Male Pattern Hair Loss and cumulative clinical and laboratory safety data for 2287 patients.

Additionally, serious adverse experiences (AEs) reported from ongoing Male Pattern Hair Loss studies through January 15, 1997 are provided.

Based on the data for the additional 6-month reporting period in this SUR from the five Male Pattern Hair Loss studies, there is no evidence to suggest that there is an increased incidence of AEs with greater duration of therapy. Thus, the safety data for finasteride presented in this SUR support the overall favorable safety and tolerability profile of finasteride presented in the original NDA and in the proposed product label.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.

Attachment
Federal Express #1

Desk Copy: (Cover letter only) Ms. Robin Anderson, Project Manager, HFD-540, CRP2 N-248, Federal Express #1

q\murakami\propecia\fda-ltr5.doc

DUPLICATE

Larry P. Bell, M.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2310
215 652 5000

January 15, 1997

NEW CORRESPONDENCE

REVIEWS COMPLETED
ACTION
LETTER E-MAIL MEMO
DATE

MERCK
Research Laboratories

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 16 1997
HFD-

Mr. David M. Moss
Director, Division of Information Systems Design
Center for Drug Evaluation & Research
Food & Drug Administration
5600 Fishers Lane, 8B-11
Rockville, Maryland 20857

Original New Drug Application (NDA)
NDA 20-788: Tablets PROPECIA™ (Finasteride)
Delivery of *StorageWorks* Building Block (Hard Disk) to DISD

Dear Mr. Moss:

By copy of this letter, Merck Research Laboratories (MRL) is providing to the Division of Information Systems Design (DISD) a *StorageWorks* Building Block (Serial Number NI624B9500), hereafter referred to as the hard disk, which contains the Original New Drug Application (NDA) for PROPECIA™ (Finasteride) in the treatment of Male Pattern Hair Loss. This hard disk is to be installed on the MRL-dedicated network server at the Agency. It is Merck's anticipation that the hard disk will be installed in a timely manner after delivery of the hard disk to DISD.

The reviewers from the Division of Dermatologic and Dental Drug Products (DDDDP) and Division of Scientific Investigation (DSI) who should be provided access to the electronic submission from their desktops are as follows:

Ms. Robin Anderson	Project Manager	DDDDP	CRP2 N240	301-827-2042
Dr. Javier Avalos	Pharmtox.	DDDDP	CRP2 N221	301-827-2024
Dr. Jose Carreras	Clinical Audit	DSI	MPN1 119	301-594-1032
Dr. Valeria Freidlin	Biostatistics	DDDDP	CRP2 N250	301-827-2081
Dr. Joel S. Hathaway	Chemistry	DDDDP	CRP2 N237	301-827-2040
Dr. Barbara Hill	Pharmatox.	DDDDP	CRP2 N223	301-827-2069
Dr. Hon Ko	Medical	DDDDP	CRP2 N223	301-827-2022
Mr. Rodney Smith	Computer Resources	DDDDP	PKLN 8B45	301-827-3276

Please notify MRL's Regulatory Agency Relations (RAR) Office (301/881-9000) when the disk installation is successfully completed and access from the reviewers' desktops is functional.

When an action has been taken on the PROPECIA™ (Finasteride) original NDA and the hard disk is no longer needed, MRL will make arrangements to retrieve it from the FDA. The FDA will be responsible for the "sanitization" of the hard disk (Serial Number NI624B9500) before MRL removes it from CDER. We further understand that, in the future, information submitted in electronic form may be retained indefinitely by the Agency as an archival copy of the application, in the event that a complete paper submission is not filed.

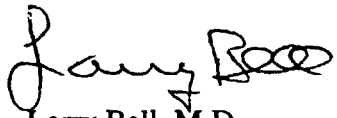
We have taken precautions to ensure that any software on this hard disk is free of computer viruses and we authorize DISD to use anti-virus software, as appropriate.

There are five attachments to this letter:

Attachment 1	A Table of Organization of the contents of the accompanying electronic submission.
Attachment 2	A Difference Report of differences between the electronic version of this submission and the hard copy submission identified.
Attachment 3	Installation Instructions detailing how to install the hard disk in the server.
Attachment 4	Documentation regarding the development procedures performed at MRL for this electronic submission.
Attachment 5	A complete list of file names.

During the time that the hard disk is actively being used, MRL will provide technical support. Any questions relating to this hard disk should be addressed to me (610/397-2310) or, in my absence, Marie A. Dray (301/881-9000).

Sincerely,



Larry Bell, M.D.
Director, Regulatory Affairs

Attachments (5)
StorageWorks Building Block (Serial Number NI624B9500)
Federal Express #1

cc (cover letter only):

Chief
Document Management and Reporting Branch, HFD-53
Federal Express #2

Mr. G. Brolund
Chief, Information Systems Branch One, HFD-72
Federal Express #3

Mr. M. Buster
Chief Systems and Network Section, HFD-72
Federal Express #3

Mr. K. Edmunds
Assistant to the Director, Division of Information Systems Design (DISD), HFD-70
Federal Express #4

cc (cover letter only):

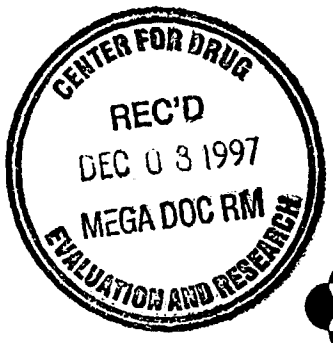
LIST OF REVIEWERS

Ms. R. Anderson	HFD 540, CRP2 N240, Federal Express #5
Dr. J. Avalos	HFD 540, CRP2 N221, Federal Express #5
Dr. J. Carreras	HFD 340, MPN1 119, Federal Express #6
Dr. V. Freidlin	HFD 725, CRP2 N250, Federal Express #7
Dr. S. Hathaway	HFD 540, CRP2 N237, Federal Express #5
Dr. B. Hill	HFD 540, CRP2 N223, Federal Express #5
Dr. H. Ko	HFD 540, CRP2 N223, Federal Express #5
Mr. R. Smith	HFD 760, PKLN 8B45, Federal Express #8

cc (cover letter with attachments):

NDA 20-788, HFD-570 (2 copies), Federal Express #9 (as above)

ORIGINAL



Merck & Co., Inc.
West Point PA 19486

Orig.

BL

MERCK
Research Laboratories

December 8, 1997

Jonathan Wilkin, M.D., Director
Division of Dermatologic Drug Products
HFD-540, Room N-214
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 20-788: PROPECIA™
(Finasteride)

Dear Dr. Wilkin:

Reference is made to the above New Drug Application and a submission of proposed alternate product labeling on December 2, 1997 by Merck Research Laboratories (MRL). It was noted in the December 2nd proposal that the figure entitled "Effect on Hair Count" was subject to further revision (e.g. axis dimensions, line labels, etc.).

By this letter and attachments, MRL is providing the revised figure with expansion of the x-axis in the extension phase and including the treatment definitions with each line. A hard copy of the new figure is attached. A diskette (in WP) with the proposed product circular incorporating the revised figure and the Patient Package Insert (as previously submitted) is also enclosed for Ms. Kummèrer and Dr. Ko.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information, please contact Robert E. Silverman, M.D., Ph.D. (610/397-2944) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely,

Marie Addary for
Robert E. Silverman

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

q/ligi/letters/fda/res

Attachment
Desk Copy: Dr. Hon Ko, HFD-540, CRP2 N223, Hand Delivered
Ms. Susan Kummerer, HFD-540, CRP2 N240 (Diskettes included, 2 copies) Hand Delivered

Merck & Co., Inc
West Point PA 19486

BL

DRUG AMENDMENT

DUPLICATE

MERCK
Research Laboratories

December 2, 1997

Jonathan Wilkin, M.D., Director
Division of Dermatological Drug Products
HFD-540, Room N-214
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 20-788: PROPECIA™
(Finasteride)

Dear Dr. Wilkin:

Reference is made to the above New Drug Application; a telefax from FDA on November 21, 1997 containing the Agency's suggested text for the product circular and patient package insert for PROPECIA™; and a previous submission on December 1, 1997 via telefax by Merck Research Laboratories (MRL) of a label counterproposal.

Attached is an updated counterproposal for the label that contains a few editorial changes from the December 1 fax submission. This draft supercedes the December 1 submission and is provided as both a side-by-side presentation (FDA revised circular on left, MRL response on right) in Attachment 1 and clean running text of the complete counterproposal in Attachment 2. Many of the Agency's suggested revisions have been incorporated by MRL in this counterproposal. However, in some cases MRL has offered alternative wording. MRL is providing, below, additional discussion on some of the substantive changes to the Agency's revised circular included in the MRL counterproposals.

<u>Neutrogena T-Gel</u> (Attachment 1; pp. 5, 6, 7, 8, 9, 10, 18)

MRL believes it is appropriate that the use of a medicated, tar-based, shampoo by <u>all</u> participants in the clinical trials for PROPECIA™ should be presented in the product

label. This fact is now explicitly stated at the beginning of the Clinical Studies section along with the rationale for its use in the attached counterproposal. However, MRL also firmly believes that the repeated citation of the shampoo use throughout the description of the clinical studies and its inclusion in the Indication is unjustified.
The Agency's previously stated concern that the tar-based shampoo might stain otherwise cosmetically unimportant hairs prompted MRL to conduct the "T-Gel study" (Protocol #110) which documented that there was no statistically significant effect on hair counts by this shampoo using the MRL methodology for hair counting (see letter to NDA 20-788 on November 11, 1997).

At the November 13, 1997 Advisory Committee meeting, the Agency raised a question as to the potential interaction of the shampoo with PROPECIA™ on a biologic basis, suggesting that the shampoo might influence (i.e., enhance) the mechanism of action on hair regrowth by finasteride. Neither the Agency representatives, expert dermatology consultants nor dermatologists on the Committee could offer any data nor a plausible theoretical basis to support this concern, particularly in light of the consistent use of the shampoo by both treated and placebo patients.

Scalp Location Identification (Attachment 1; pp. 5, 8, 10)

MRL acknowledges the Agency's acceptance of demonstrated efficacy by PROPECIA™ in the Phase III "Frontal" Study (Protocol #092). As discussed previously, MRL also appreciates the Agency's concern about the description of the scalp area included in the study. To increase the precision of the label description, MRL has now proposed that the specific Norwood/Hamilton classification at baseline for the men studied in all the Phase III studies (Protocols #087, #089 and #092) be included. The proposed descriptive term for the area of scalp examined in Protocol #092 is "anterior mid-scalp (frontal)". The term "frontal" is retained parenthetically since it is the specific term used in several of the patient and investigator assessment tools.

Further, MRL believes that the Agency's draft label of November 21 inappropriately specifically excludes efficacy in "frontal baldness". The results of multiple measures in Protocols #087, #089 and #092, including the patient self assessments and Savin scale assessments, establish that both patients and investigators felt that improvement in the "frontal" area (the term specifically used in the assessment questions) was apparent.

Effect on the Balding Process (Attachment 1; pp. 3, 5, 9, 10)

MRL acknowledges the Agency's concern with the original proposal for inclusion of the phrase "prevent further hair loss" in the Indications section of product label. Accordingly, we feel that the phrase "retards further balding" more correctly describes the

results observed in the three Phase III trials. MRL believes that the totality of the available information including the data from the finasteride and placebo treated patients in the MRL development program for PROPECIA™, the preexisting pre-clinical and clinical information on the function of DHT and the accumulated information provided by investigation of the genetic syndrome of 5α-Reductase deficiency establish that the reduction of DHT induced by finasteride directly interrupts a central factor in the development of androgenetic alopecia. By this mechanism, finasteride stimulates the regrowth of miniaturized hair follicles and inhibits further miniaturization which are characteristics of the progressive balding process. These mechanistic conclusions are relevant to the prescriber and, therefore, are summarized in the Clinical Pharmacology and Indications sections of the attached counterproposal.

Age (Attachment 1, pp. 5, 10)

MRL agrees that the age range of the men involved in the clinical trials for PROPECIA™ should be clearly provided in the product circular. This is included in the introduction to the Clinical Studies section of the MRL counterproposal.

As stated by many of the dermatologists at the Advisory Committee meeting (both consultants and members), the process of androgenetic alopecia is not restricted to the age group 18-41. The use of specified age groups during clinical trials of other pharmaceuticals for conditions which occur beyond the specified age group (e.g., topical minoxidil) have not prompted notation of the age group (as an implicit limitation) in the Indications section of the product circular. Therefore, the attached counterproposal does not include the age range in the Indications section.

Ethnic Analysis (Attachment 1; pp. 9-10)

MRL believes the Agency's November 21 proposal significantly over-emphasizes the subgroup analysis for ethnic differences. We have, therefore, proposed a more succinct narrative description that conveys the conclusions that the Agency has embraced.

Ejaculate Volume (Attachment 1; pp. 4, 16)

MRL agrees that the results on ejaculate volume from earlier studies in men taking finasteride 5 mg should be accurately presented in the product circular and in a consistent fashion to the presentation in the FDA approved label for PROSCAR™. MRL has offered an alternative description for the results from Protocol #094 for this parameter that provides the relevant specific data in the Clinical Pharmacology section of the circular.

Sexual Function Questionnaire (Attachment 1; pp. 13-14, 16)

MRL believes the Agency's November 21 proposal significantly over-emphasizes the results of the questionnaire in light of the clearly stated sexual adverse event profile that is included in the Adverse Events section of the label. Further, the Agency's proposal is imprecise and potentially misleading since the results of the global satisfaction question ("Overall, during the last 30 days, how satisfied have you been with your sex life?") showed no significant difference between placebo and finasteride treated groups. Therefore, MRL has deleted the tabular presentation of the questionnaire results proposed by the Agency and replaced it with a more succinct narrative summary in the Adverse Reactions section.

Adverse Reactions Section (Attachment 1; p. 17)

MRL appreciates the Agency's interest in communicating the safety profile for finasteride demonstrated in the current PROSCAR™ label. However, MRL believes that inclusion, in toto, of the Adverse Reactions section of the PROSCAR™ label is not warranted particularly since the PROSCAR™ experience does not demonstrate a major difference in the nature or level of severity compared to the adverse experiences seen with PROPECIA™. Nonetheless, MRL has proposed, in the attached draft, to expand upon the previous brief description of the PROSCAR™ experience.

Labeling Taken From the Circular for PROSCAR™ (Attachment 1; pp. 1, 4, 12, 13, 14, 15, 16)

Several parts of MRL's original label proposal for PROPECIA™ were extracted directly from the currently approved circular for PROSCAR™ (finasteride 5 mg). The Agency has chosen to revise some of these elements in the proposed circular for PROPECIA™. MRL believes it is inappropriate and confusing to the prescriber to have inconsistency in the presentation of information between the PROPECIA™ and PROSCAR™ labeling. Therefore, MRL has proposed a return to the previously FDA approved version. MRL is willing to entertain the development of a consensus change for both product labels but believes that this matter would be best dealt with in the post-approval stage for PROPECIA™.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Marie Aday for
Robert E. Silverman

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

q/mcs/ltr/523

Attachment

Hand Delivered

Desk Copy: Dr. Hon Ko, HFD-540, CRP2 N223, Hand Delivered
Ms. Susan Kummerer, HFD-540, CRP2 N240, Hand Delivered

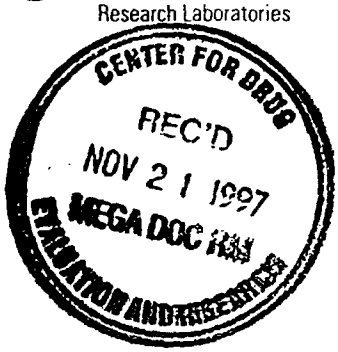
Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

November 20, 1997

BL

MERCK
Research Laboratories



Jonathan Wilkin, M.D., Director
Division of Dermatological Drug Products
HFD-540, Room N-214
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Dear Dr. Wilkin:

Amendment to Pending New Drug Application

NDA 20-788: PROPECIA
(Finasteride)

With this letter we are providing a draft labeling amendment for FDA approval. These drafts amend and replace the labeling components submitted with the original NDA cited above on December 20, 1996. The labels have been revised to include new warning text, addition of a 1-800 number and PROPAK™, new artwork and numerous format changes, including the Trade logo.

Attached are the following Trade items:

- Bottle Label, Unit of Use 30's
- Bottle Label-3 X 30, PROPAK™ Three 30 Tablet Bottles
- Carton for 3 X 30 PROPAK™

We consider the information included in this amendment to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

Attachment
Federal Express #1

q:\sax\mur\20788\draftcar.doc

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

DESK COPY

November 19, 1997

MERCK
Research Laboratories

Jonathan Wilkin, M.D., Director
Division of Dermatological Drug Products
HFD-540, Room N-214
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Dear Dr. Wilkin:

NDA 20-788: PROPECIA
(Finasteride)

Reference is made to the above New Drug Application (NDA) and the meeting of the Dermatologic and Ophthalmologic Drugs Advisory Committee meeting on November 13, 1997. During the November 13 meeting, Merck Research Laboratories (MRL) showed slides in response to questions that were not included in the hard copy collection of slides distributed by MRL at the start of the meeting. By attachment, MRL is now providing hard copies of these additional slides; eleven related to efficacy and nine related to safety.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

mcs/q/ltr/516

Attachment
Federal Express #1
Desk Copy: Dr. Hon Ko, HFD-540, CRP2 N223, Federal Express #1
Ms. Susan Kummerer, HFD-540, CRP2 N240, Federal Express #1
Ms. Tracy Riley, HFD-21, Chapman Bldg., Rm. 200, Federal Express #2

Robert E. Silverman, M.D., Ph.D
Senior Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

December 19, 1997

MERCK
Research Laboratories

Jonathan Wilkin, M.D., Director
Division of Dermatological and Dental Drug Products
HFD-540, Room N-214
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 20-788: PROPECIA™
(Finasteride)

Dear Dr. Wilkin:

Reference is made to the above New Drug Administration (NDA) and a teleconference between the Agency and Merck Research Laboratories (MRL) on December 18, 1997. In follow-up to this teleconference, MRL is, herein, providing the agreed upon revised product labeling (product circular and patient package insert). Attached are: (1) side-by-side presentations with the Agency's proposals of December 17, 1997 on the left and the annotations of changes in the right column; and (2) the clean running text. Also attached is a copy of the current PROSCAR PPI, as requested. Two copies of a diskette in PDF format of the clean running texts are also enclosed for Ms. Kummerer.

During the December 18 discussion, there was agreement to move the description of the sexual function questionnaire to the Clinical Pharmacology section but the exact location was not determined. You will note that the description appears just before the Pharmacokinetics sub-heading in the attached proposal.

By this letter, we are also documenting the submission by telefax on December 18, 1997 of Appendix 14 from Protocol #012 that was originally submitted to the Agency on February 7, 1994, as part of a supplemental NDA to PROSCAR (NDA 20-180).

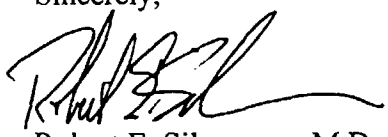
During the teleconference on December 18, MRL committed to work with FDA (Division of Dermatological and Dental Drug Products and Division of Reproductive and Urological Drug Products) on the label to insure consistency between the approved PROSCAR label and the PROPECIA label. This will apply to the following sections of the PROPECIA circular: CLINICAL PHARMACOLOGY (*Pharmacokinetics* subsection), and PRECAUTIONS (*Drug Interactions, Carcinogenesis, Mutagenesis, Impairment of Fertility* and *Pregnancy* subsections). This letter confirms our verbal

commitment to work with both Divisions to reach consensus for consistent labeling between the two products after the approval of PROPECIA.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,



Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

q/mcs/ltr/531

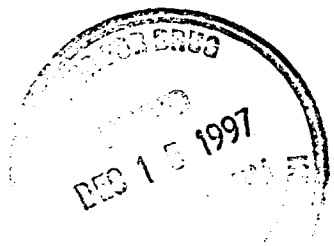
Attachment
Hand Delivered
Desk Copy: Ms. Susan Kummerer (with diskettes), HFD-540, CRP2 N240

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

December 12, 1997

MERCK
Research Laboratories



Jonathan Wilkin, M.D., Director
Division of Dermatological Drug Products
HFD-540, Room N-214
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 20-788: PROPECIA™
(Finasteride)

Dear Dr. Wilkin:

Reference is made to the above New Drug Application; a product labeling proposal submitted by Merck Research Laboratories (MRL) on December 2, 1997; and telephone conversations on December 10, 1997 between Dr. Silverman and Drs. Ko, Weintraub and Ms. Kummerer. In follow-up to the December 10 conversations, MRL is herein providing a revised labeling proposal (attached; previously faxed to the Agency on December 11) and comments on two issues; reference to Neutrogena T Gel in labeling; and changing the tradename for PROPECIA.

Neutrogena T Gel

As previously discussed with the Agency, incorporation of the standardized use of Neutrogena T-Gel shampoo by all patients (placebo and finasteride treated) in the Phase III trials with PROPECIA was the result of recommendations from expert dermatologists during the planning process for these trials. The recommendation was based on the consultants' opinions that specific use of a mild OTC tar-based shampoo would minimize seborrheic dermatitis, a condition not uncommon in balding men, which might effect the hair count results seen in the studies.

FDA has recommended that the use of this shampoo be cited throughout the product circular for PROPECIA. This is based on two concerns raised by FDA following the completion of the Phase III program. Initially the Agency was concerned that the shampoo might have stained cosmetically unimportant hairs and, thereby, compromised

the validity of our hair count methodology (raised to MRL during the Ninety-Day meeting on March 13, 1997). MRL responded by performing a clinical study directly addressing this issue (see below). Subsequently, the Agency expressed another question whether the shampoo might have influenced (i.e., enhanced) the mechanism of action on hair growth of finasteride (raised to MRL at the Advisory Committee meeting for PROPECIA on November 13, 1997).

MRL agrees with inclusion of a description of the use of medicated shampoo in the general introductory discussion of the clinical trials in the CLINICAL PHARMACOLOGY section of the product circular. However, MRL maintains its position that reference to the use of a medicated, tar-based shampoo in the INDICATION or DOSAGE AND ADMINISTRATION sections is unwarranted. This position is grounded on two independent but complimentary premises: the scientific evidence and broad regulatory precedent.

Scientific Evidence: There are three lines of evidence, that MRL has previously shared with the Agency, which support MRL's proposal for product labeling on this issue. (1) The demonstration of efficacy for PROPECIA has been measured as a difference between treated and placebo groups. All patients (both finasteride and placebo treated) used the same shampoo. (2) Progressive hair loss was seen in the placebo group while using the medicated shampoo. In addition, hair loss, back to baseline, was seen in those patients switched from finasteride to placebo (while maintaining the use of the medicated shampoo) in the extensions of the Phase III pivotal studies. (3) In specific response to the Agency's first concern about possible shampoo related staining of hairs, MRL completed an ancillary study (Protocol #110). The preliminary results of this cross-over study have been previously reported to the Agency (November 11, 1997) and documented that there was no statistically significant effect on hair counts by this shampoo using the MRL methodology for hair counting.

The Agency's concerns were raised to MRL in a hypothetic context. Neither the Agency representatives, expert dermatology consultants nor dermatologists on the FDA's Advisory Committee could offer any data nor a plausible theoretical basis to support either of the Agency's concerns.

In summary, the data generated by MRL in the development program for PROPECIA in conjunction with the absence of data in the literature suggesting an effect of tar-based shampoo on the process do not support any concern that the standardized use of the shampoo influenced the demonstrated efficacy of PROPECIA.

Regulatory Precedent: During the December 10 conversation, Dr. Weintraub expressed his perception that the inclusion of the medicated shampoo in the INDICATION and DOSAGE AND ADMINISTRATION sections of the product circular would be an analogous situation to the inclusion of references to the concomitant use of appropriate diet in the product labeling for cholesterol lowering agents. MRL does not agree. In the

case of diet for the treatment of cholesterol disorders, there is strong and broadly accepted evidence of independent efficacy for diet in the management of these disorders. In fact, the National Cholesterol Education Program (NCEP) specifically recommend that appropriate diet be initiated before pharmacologic therapy is begun and that this diet be maintained during pharmacologic therapy. Our data (see above) suggest that medicated shampoo does not have any independent effect on androgenetic alopecia nor is there literature to suggest that it does.

MRL believes that there are, in fact, many more analogous examples in FDA approved product labeling to support the lack of necessity for reference to the shampoo in product labeling. In these cases, concomitant modalities were used in clinical trials but reference to these were not required in product labeling. These include: (1) FOSAMAX for osteoporosis where supplemental dietary calcium was used in major endpoint studies; (2) ZOCOR for reducing the risk of serious cardiovascular events where low dose aspirin was used in a majority of patients; (3) many H_2 blockers for treatment of ulcers, GERD, etc., where low potency antacids were used; and (4) antidepressants where concomitant psychotherapy was included in clinical studies. These examples are particularly striking because, in each case, the coincident treatment is accepted to have potentially relevant impact, alone, on the condition involved (which is not true for medicated shampoo in androgenetic alopecia) but specific labeling was, nonetheless, deemed unnecessary. In the cases where MRL has specific knowledge, documentation of the equivalent use of the coincident treatments by the placebo group was the foundation for the labeling decisions.

Changing the Tradename for PROPECIA

During the December 10 conversation, Dr.Weintraub reported that the Agency is in a process of internal review of policies related to the tradenaming of products with equivalent active ingredients. Dr. Weintraub suggested that this issue might apply to this NDA. Merck & Co. believes that the PROPECIA trademark is appropriately established based on two independent and complimentary premises: the timeliness of this issue in the context of the current NDA review; and the medical rationale for the distinction between PROPECIA and PROSCAR.

Timeliness: MRL was informed by Ms. Robin Anderson, Project Manager, on April 23, 1997, that the Agency's Nomenclature Committee had found PROPECIA to be an acceptable trademark for finasteride 1 mg. Since that time, Merck & Co. has invested major effort and resources to establish this trademark on a world-wide basis and prepare all the necessary materials to market this drug under the approved trademark. There has been no suggestion that the selection of this trademark raises safety concerns. On the contrary, Merck believes that safety concerns favor the use of a tradename distinct from PROSCAR (see below). Therefore, Merck & Co. believes there is no compelling reason to initiate a tradename change for PROPECIA at this point in the NDA review process.

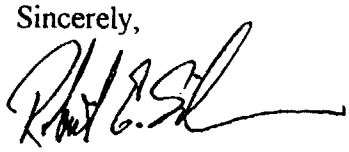
Medical Rationale: Merck & Co., Inc. carefully considered the issue of establishing a distinct tradename for finasteride 1 mg several years ago. It was our conclusion that using the established trademark of PROSCAR would engender confusion in patients and prescribers that might result in overdosing in men with androgenetic alopecia and splitting of the higher dose pills, which is a particular issue for cutaneous exposure to the active ingredient for women. Therefore, we concluded that a distinct trademark was appropriate for a dosage with an indication and patient population that was distinct from PROSCAR.

As always, MRL would welcome an opportunity to participate with FDA and the industry, in general, in the process of assessing current policy in this area and developing new policy for the future.

We consider this information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information, please contact Robert E. Silverman, M.D., Ph.D. (610/397-2944) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely,



Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

q/mcs/ltr/529

Attachment
Desk Copies: Dr. Hon Ko, HFD-540, CRP2 N223, Federal Express #1
Ms. Susan Kummerer, HFD-540, CRP2 N240, Federal Express #1
(Fax) Dr. Michael Weintraub, HFD-105, CRP2 S219, Federal Express #2
(Fax) Ms. Mary Jean Fornaro, HFD-540, CRP2 N240, Federal Express #1

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

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not desk copies.

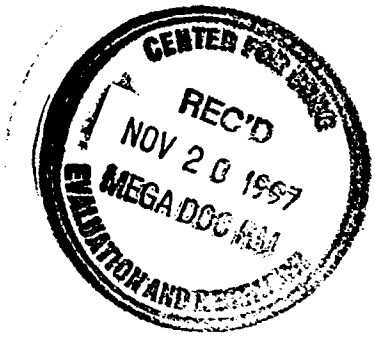
Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

NC
NEW CORRESP
ORIGINAL

November 19, 1997

MERCK
Research Laboratories

Jonathan Wilkin, M.D., Director
Division of Dermatological Drug Products
HFD-540, Room N-214
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850



Dear Dr. Wilkin:

NDA 20-788: PROPECIA
(Finasteride)

Reference is made to the above New Drug Application (NDA); the meeting of the Dermatologic and Ophthalmologic Advisory Committee on November 13, 1997 and telephone conversations between Dr. Silverman and Dr. Ko on November 14 and 17, 1997. In follow-up to the November 14 and 17 conversations, Merck Research Laboratories (MRL) is providing, at the Agency's request, additional information related to issues raised during the Advisory Committee meeting. In addition, MRL would like to summarize our perspectives on a number of issues discussed during the meeting.

Efficacy Issues

The meeting discussion particularly addressed the efficacy in the frontal region of the scalp. Notably, a major issue appeared to be the appropriate terminology to be used in describing the location of the demonstrated efficacy outside the vertex area (e.g., "frontal"). Given the systemic administration of finasteride and the generalized lack of androgenetic alopecia (AA) in men with a genetic deficiency of 5α-Reductase, efficacy of finasteride throughout the scalp areas involved with AA should be expected. During the Advisory Committee meeting, MRL presented results from the NDA for the Phase III Frontal study that established efficacy in that scalp region by four different measures. In addition, as mentioned during the meeting, the Phase III Pivotal studies included global photographic assessments by the expert panel from not only the vertex view but also three other views; superior/frontal (comparable to the primary view assessed in the Phase III Frontal study), anterior hairline and temporal hairline. The vertex view was predefined as a secondary endpoint and was included in the NDA while the latter three were exploratory. As requested, the results from these other three views at 12 months and 24

months are provided in Attachment 1 and 2, respectively. These results corroborate the demonstrated efficacy in the frontal region seen in the Phase III Frontal Study. Since much of the meeting discussion centered around the definition of "frontal", MRL looks forward to working with the Agency to consider alternative terminology to "frontal" in the product circular to describe the location of the demonstrated efficacy beyond the vertex area.

Another issue of substantial discussion at the meeting concerned the proposed INDICATION language on prevention of further hair loss. MRL strongly holds that the existing data support a label statement that this treatment alters (e.g., "slows") the underlying process of AA. MRL believes that appropriate language can be found to convey this message and looks forward to working with the Agency in the upcoming label negotiations to reach a consensus on this point.

Safety Issues

A number of issues regarding the safety of long term use of finasteride 1 mg in young men were discussed. MRL believes that several general and specific comments need re-emphasis in follow-up to the meeting. The specific issues include hormonal specificity, bone changes, prostate cancer and fertility.

General Comments

- Preclinical Toxicology: The Agency has previously reviewed, in the context of NDA 20-180 (PROSCAR), an extensive body of pre-clinical information derived from long term studies in multiple species directed at questions of acute and chronic toxicity, carcinogenicity, and developmental and reproductive toxicology. The current approved circular for PROSCAR™ contains a summary of these studies. The results of these preclinical studies established that the only significant toxicity is due to the exposure of the developing male fetus, as would be predicted by the mechanism of a 5α-Reductase inhibitor. Notably, there were no adverse effects related to cancer or fertility.

- Genetic Syndrome of 5α-Reductase Deficiency: As discussed by Dr. Imperato-McGinley, the use of finasteride creates a virtual surrogate for the genetic syndrome of 5α-Reductase deficiency in adults. The long-term general good health of men with the genetic syndrome, beyond the sequelae of in utero deficiency, attests to the long-term safety of treatment with finasteride.

Specific Comments

Hormonal Specificity: Finasteride is a highly specific inhibitor of 5α-Reductase. At the clinical dose, and many times the clinical dose in animals for extended periods, the

compound has no other demonstrable effects on any steroid hormone action or metabolism. This issue has been exhaustively studied in both animals and man as documented a number of years ago in the approved NDA 20-180 (PROSCAR). The attribution of muscle toxicity in a case report of "glucocorticoid-like" myopathy in a single patient on finasteride cited by the Agency at the meeting is not supported by the accumulated safety database with PROSCAR or PROPECIA.

- Bone Changes: During the Advisory Committee meeting, MRL briefly summarized the results of the monitoring of bone mineral density (BMD) from PLESS, the recently completed 4 year trial with PROSCAR that has been submitted to NDA 20-180 (PROSCAR) in support of a label change for PROSCAR. Treatment of finasteride 5 mg in these older men did not adversely effect BMD in concordance with the results reported in the NDA for PROPECIA. As requested by the Agency, excerpts from the PLESS submission that summarize the relevant data on this issue and other safety questions (i.e., breast changes, prostate cancer) raised during the meeting can be found in Attachment 3.

- Prostate Cancer: As Dr. McConnell summarized at the meeting, all the data from both pre-clinical and clinical sources support the lack of risk for prostate cancer from treatment with finasteride. In fact, Dr. McConnell reported that the NCI is currently engaged in a large, long-term study designed to test the hypothesis that chronic use of finasteride may prevent prostate cancer. As discussed by Drs. McConnell and Scolnick, the published report, cited by Dr. Ko at the meeting, of a cell line derived from a human prostate cancer, LnCaP, that is stimulated by finasteride has virtually no clinical relevance. This cell line was specifically selected under in vitro conditions of complete androgen deprivation which are not remotely equivalent to the environment of a clinical situation.

  Fertility: There was substantial overlapping discussion on the potential for adverse effects on fertility in men taking finasteride 1 mg and the related but independent issue of changes in ejaculate volume. As Dr. Overstreet stated at the meeting, ejaculate volume changes of the magnitude seen in men treated with finasteride are not meaningful surrogates for altered fertility. He pointed out that the observed changes were within the range of normal variability and that the ejaculate volumes remained within the normal range.

  As Dr. Overstreet discussed, there is no evidence to suggest the potential for an impairment in male fertility from treatment with finasteride 1 mg. He pointed out that no clinically significant effects were observed between treatment groups for the predefined semen parameters (including ejaculate volume) in the Finasteride 1 mg Safety Study (Protocol #094). Further, he stated that the lack of any effects of finasteride on male fertility is supported by a body of preclinical animal data in several species treated chronically at high doses; by the findings in patients with genetic 5α-

Reductase deficiency who have successfully fathered normal children despite lifelong deficiency of DHT (corroborated by Dr. Imperato-McGinley); and by the larger number of reported pregnancies in finasteride (N=37) compared to placebo (N=10) patients in the male pattern hair loss program, despite the early prohibition against fathering children in the clinical trials at the time of these reports. All live births were without congenital anomolies.

The Agency raised an issue on the significance of the measured changes in ejaculate volume seen in Protocol #094. The power to see differences between treatment groups in the secondary endpoint of ejaculate volume was outlined in both the protocol and in a separate data analysis plan developed prior to unblinding. In 2 previous studies with finasteride at the 5 mg dose (Protocols #012 and #056), we observed a reproducible and reversible median decrease of approximately 25% in ejaculate volume in treated subjects. In Protocol #094, we predefined the *minimally* clinically important difference as being 10% between treatment groups. This was a highly conservative stipulation based on both the results observed at the 5 mg dose as well as the wide biological variability in ejaculate volume observed in placebo patients. It was not based on any evidence to suggest that a 10% change was clinically meaningful for fertility. In retrospect, this stipulation was a mistake as asserted by Dr. Overstreet (see above). Although the observed median results in Protocol #094 were generally comparable between treatment groups (only a 1.0% difference), the confidence interval just exceeded the predefined minimally clinically important difference of -10%. A lack of any clinical concern based on this result is supported by the fact that only 2 patients in the study, both in the placebo group, had a measured decrease in ejaculate volume below 1 mL, a value below which, experts agree, male fertility may be impaired. Nevertheless, given that we did not meet the predefined criteria to conclude that there was no change in ejaculate volume, MRL will work with the Agency to develop label language that accurately reflects the results of this study.

- PSA: As suggested at the Advisory Committee meeting, the addition to the label for PROPECIA™ of a recommendation to double the measured PSA if it is being used as part of a screening evaluation for prostate cancer, as currently included in the product circular for PROSCAR, may be advisable. As briefly discussed by MRL at the meeting, the impact of treatment with finasteride 5 mg on PSA screening was examined carefully in PLESS, as summarized in Attachment 3, and showed that the "multiply by 2" rule maintained the utility of PSA screening for prostate cancer. As Dr. McConnell offered during the meeting, application of the multiply by 2 rule for men taking PROPECIA™ would be the most conservative approach. MRL will work with the Agency to consider alterations to the proposed product labeling regarding PSA to ensure clarity.

Based on the results of the Advisory Committee meeting and discussions with the Agency, MRL anticipates that PROPECIA™ will be judged safe and effective for the treatment of

men with AA and looks forward to timely negotiations on the product labeling within the PDUFA guidelines.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

mcs/q/ltr/514

Attachment

FAX to Dr. Hon Ko (301-827-2075)

Federal Express #1

Desk Copy: Dr. Hon Ko, HFD-540, CRP2 N223, Federal Express #1
Ms. Susan Kummerer, HFD-540, CRP2 N240, Federal Express #1
Dr. Michael Weintraub, HFD-105, CRP2 S219, Federal Express #2

DUPLICATE NC

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

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Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

November 11, 1997

MERCK
Research Laboratories

Jonathan Wilkin, M.D., Director
Division of Dermatological Drug Products
HFD-540, Room N-214
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 20-788: PROPECIA
(Finasteride)

Reference is made to the above New Drug Application (NDA); a 90-day meeting held between the Agency and Merck Research Laboratories (MRL) on March 19, 1997; a submission to this NDA on May 13, 1997 by MRL of a draft protocol synopsis; a telefax from FDA on June 26, 1997 containing comments on the May 13 draft protocol synopsis; and a final protocol submitted to IND on August 14, 1997 (Protocol #110; Serial No. 111). Reference is also made to the upcoming Dermatologic and Ophthalmic Drugs Advisory Committee session on November 13, 1997, concerning the above noted NDA; and a telefax received from the Agency on November 10, 1997, containing draft questions for the Advisory Committee. At the 90-day meeting, the Agency requested that MRL examine whether the use of tar-based shampoo might have had effect on the hair count measured in the clinical studies included in the NDA. As noted above, after the exchange of a draft and comments, a final protocol was submitted to evaluate the effect of tar-based shampoo on hair counts.

Protocol #110 has just been completed and unaudited data are now available. MRL is making these preliminary results available to the Agency, at this time, because a direct question of relevance to this study has been raised by the Agency in their draft questions to the Advisory Committee (Question 1.1). In anticipation that this specific question will engender discussion at the November 13 session and in order to allow the Agency to review this data prior to the November 13 session, MRL is providing, by attachment, a brief report of the unaudited results of Protocol #110. There was no statistically significant effect on hair counts seen in this study due to tar-based shampoo versus anti-residue shampoo. In our experience, final auditing of this data is unlikely to change this conclusion.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

cs/q/ltr/521

ttachment

ederal Express #1

esk Copy: Dr. Hon Ko, HFD-540, CRP2 N223, Federal Express #1

Ms. Susan Kummerer, HFD-540, CRP2 N240, Federal Express #1

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

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Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

October 22, 1997

MERCK
Research Laboratories

Jonathan Wilkin, M.D., Director
Division of Dermatological Drug Products
HFD-540, Room N-214
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

NDA 20-788: PROPECIA™
(Finasteride)

Reference is made to the above New Drug Application (NDA) and a submission to the NDA from Merck Research Laboratories (MRL) on September 25, 1997 that included an updated proposal for the product circular.

We have recently discovered that the September 25 label proposal did not include an additional sentence related to circulating levels of testosterone that MRL was proposing for the CLINICAL PHARMACOLOGY section. Therefore, MRL is providing, herein by attachment, a replacement for the September 25 proposed labeling as clean running text and text showing the revisions, in both hard copy and on a diskette (2 copies for Ms. Kummerer and Dr. Ko) in Word Perfect 6.1. The additional sentence is noted in the text showing the revisions as annotation "1a". This added sentence is the only change from the September 25 submission. We apologize for this oversight.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

mcs/q/ltr/499

Enclosures: Attachments and Diskettes
Federal Express #1
Desk Copy: Dr. Hon Ko, HFD-540, CRP2 N223, Federal Express #1
Ms. Susan Kummerer, HFD-540, CRP2 N219, Federal Express #1

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

ORIGINAL

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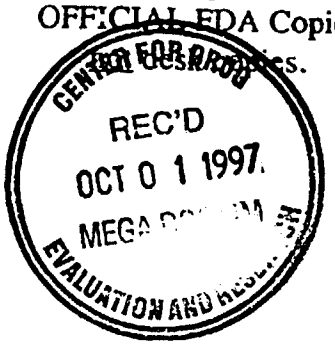
ORIG AMENDMENT

MERCK
Research Laboratories

September 30, 1997



Jonathan Wilkin, M.D., Director
Division of Dermatological Drug Products
HFD-540, Room N-214
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

NDA 20-788: PROPECIA™
(Finasteride)

Reference is made to the above New Drug Application (NDA) submitted on December 20, 1996. At the specific request of a European regulatory agency, Merck Research Laboratories (MRL) performed measurements of serum estradiol and prolactin on samples archived from Protocol 094, the Safety Study. The attached report documents the information derived from these assessments which was provided to the requesting agency.

As discussed in the attached report, the changes in estradiol and prolactin were minor and do not substantively impact on the assessment of the safety or efficacy of finasteride, 1 mg. These reassuring results will be summarized in the background package being prepared for the upcoming FDA Advisory Committee hearing on November 13, 1997. These results have not completed the standard MRL auditing process and, therefore, should be considered preliminary.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

mcs/q/ltr/536
Attachment
Federal Express #1
Desk Copy: Dr. Roy Blay, HFD-540, CRP2 N219, Federal Express #1
Dr. Hon Ko, HFD-540, CRP2 N223, Federal Express #1

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

ORIGINAL
NEW CORRES.

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P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

September 17, 1997

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EVALUATION AND RESEARCH

Jonathan Wilkin, M.D., Director
Division of Dermatological Drug Products
HFD-540, Room N-214
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

NDA 20-788: PROPECIA™
(Finasteride)

Dear Dr. Wilkin:

Reference is made to the above New Drug Application (NDA), and an Amendment to a Pending Application, which contains corrections to the electronic copy of the Original NDA for PROPECIA™ (finasteride) contained in the *StorageWorks* Building Block (SBB) delivered to Mr. David M. Moss, Director, Technology Support Service Staff (TSSS) on February 18, 1997.

With this letter we are providing an addendum to the User Training Manual that explains the use of the provisions made for direct access to the revised pages and the originals prior to revision.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

for

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

q/ltr/mcs/482
Attachment
Federal Express #1
Desk Copy: Dr. Roy Blay, HFD-540, CRP2 N219, Federal Express #1 (3 copies)
Dr. Hon Ko, HFD-540, CRP2 N223, Federal Express #1 (1 copy)
Dr. David Moss, HFD-070, Room 8B-45, Federal Express #2 (1 copy)

Merck & Co., Inc.
P.O. Box 4
West Point, PA 19486
Fax 610 397 3516
Tel 610 397 2944
215 652 5000

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August 11, 1997

MERCK
Research Laboratories

AUG 12 15 12

Jonathan Wilkin, M.D., Director
Division of Dermatological Drug Products
HFD-540, Room N-214
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

NDA 20-788: PROPECIA™
(Finasteride)

Reference is made to the above New Drug Application (NDA) submitted on December 26, 1996; and a ninety-day conference held between Merck Research Laboratories (MRL) and the Agency held on March 19, 1997 to discuss this NDA. During the March 19 meeting, MRL agreed to provide 24 month efficacy data from the Phase II and Phase III extension cohorts when they became available, as well as additional data related to haircounts and PSA among men who discontinue PROPECIA™.

By this letter and attachments, MRL is providing summary reports on the 24 month efficacy assessments for Protocol 081 (Phase IIb) and Protocols 087 and 089 (Phase III). The results of these studies demonstrate the maintenance of efficacy displayed at the one year assessments with further enhancement suggested by some parameters. In addition, the Phase III results amplify the continued hair loss in placebo treated men, thus, reinforcing the proposed claim of prevention of further hair loss by treatment with PROPECIA™. The response of the efficacy assessments to discontinuation of treatment with PROPECIA™ is shown in these Phase III results, as well. Additional safety data, beyond 12 months, from these studies were previously provided in the Safety Update Report submitted April 18, 1997. The Safety Update Report also contained preliminary data from Protocol 094 on the response of PSA to discontinuation of treatment.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

nes\q\ltr\468

Attachment
Federal Express #1
Desk Copy: Dr. Roy Blay, CSO, HFD-540, CRP2 N219, Federal Express #1 (letter only)
Dr. Hon Ko, HFD-540, CRP2 N223, Federal Express #1 (w/att.)

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
PO Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

MERCK
Research Laboratories

June 20, 1997

ORIG AMENDMENT

Jonathan Wilkin, M.D., Director
Division of Dermatologic & Dental Products
CDER, Office of Drug Evaluation V, HFD-540
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20857

NDA 20-788: PROPECIA™
(Finasteride)

Amendment to a Pending Application

Dear Dr. Wilkin:

Reference is made to the Original New Drug Application (NDA) for PROPECIA™ (Finasteride) submitted on December 20, 1996 and Amendment Applications submitted on January 24, 1997 and March 6, 1997. Also referenced is the submission of the electronic copy of the Original NDA for PROPECIA™ (Finasteride) contained in the *StorageWorks* Building Block and Replacement *StorageWorks* Building Block which were delivered to the Division of Information Systems Design (DISD) on January 15, 1997 and February 18, 1997, respectively. Merck has identified a few errors in the NDA which do not significantly change the analyses or conclusions but do necessitate corrections in several sections of the NDA including the Synopsis of Application, Clinical Documentation, Chemical and Pharmaceutical Manufacturing and Control Documentation, and Samples, Methods Validation and Label of the hard copy and electronic submissions, as follows.

Merck Research Laboratories (MRL) has identified corrections to the Clinical Study Report for Protocol 094, entitled *A Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety of Low-Dose Finasteride in Male Volunteers.* Protocol 094 investigated the effect of finasteride on bone density and indices of bone metabolism (Clinical Documentation, Reference D-8). In the original marketing application, the urinary cross-linked N-telopeptide of the type I collagen (NTX) data were reported using percent change from baseline concentration of NTX in pmol BCE/mL. It is more appropriate, however, for NTX to be corrected for urinary creatinine, which is measured simultaneously with NTX. Based on this corrected analysis,

NTX at Week 48, in units of nmol BCE/mmoL creatinine, decreased % from baseline in subjects treated with finasteride 1 mg/day compared with a % decrease in the placebo group (p=0.047). The magnitude of effect is less than that previously reported in the marketing application (-43.1% with finasteride vs. -11.3% with placebo), although the conclusions remain the same. This has resulted in the need to correct several graphs, tables and text in the CSR for this study, as well as in Item 2 (Synopsis of Application) and in the Item 8 summaries (Clinical Documentation) where these data are presented. Importantly, these changes do not affect the conclusions of this study.

MRL also has identified corrections to the Clinical Study Report for Protocol 089, entitled, *A Double-Blind, Placebo-Controlled, Multicenter Study to Determine the Effect of Finasteride on Hair Loss in Men with Androgenetic Alopecia (Male Pattern Baldness).* Appendix 4.1.62 was modified to reflect the correct data source and added as an appendix reference to Table 47. This revision of the Clinical Study Report for Protocol 089 (Clinical Documentation, Reference D-6), does not affect any other sections of the PROPECIA™ NDA.

Merck has also identified corrections to Item 3, Chemical and Pharmaceutical Manufacturing and Control Documentation, Summary I., Section E., Methods Validation. Under E.1.c., the L-number of the reference standard was corrected to read L-652.931-000D068 instead of L-653.931-000D068. In addition, the weight percent value has been revised to reflect that it is on the "as is" basis, not anhydrous and solvent-free. Under E.1.d.1, the text referring to 1,2-dihydro finasteride as a potential degradate was deleted; the compound is a potential process impurity. Under E.1.d.4, analytical data for the impurity, which is a potential degradate of finasteride, have been added.

The corrections to Item 3 also apply to Item 4, Samples, Methods Validation and Labeling, Summary I., Section E., Methods Validation as the exact pages are repeated in Item 4.

With this letter, MRL is specifically submitting revised documentation. Tabular summaries of the revisions follow this letter (behind the respective tab). Thirty-three pages have been revised and are being submitted to the Agency (in duplicate) with this letter. Since the original documentation may have been double-sided, some replacement pages will not contain any revisions. Therefore, a total of 42 pages are attached for replacement in the Original NDA.

Additional copies are being submitted to Ms. Robin Anderson for distribution to the appropriate Agency personnel for replacement in the review copies of the Original NDA. We apologize for any inconvenience the replacement of these pages may cause to your personnel.

Corrections to the electronic submission associated with the above referenced documentation will be incorporated into the *Storage Works* Building Block that contains the original electronic

version of the Original NDA for PROPECIA™. These electronic corrections will be submitted to the Division of Information Systems Design (DISD) in approximately two weeks.

Questions concerning this submission should be addressed to Robert E. Silverman, M.D., Ph.D. (610/397-2944) or, in my absence, to Bonnie J. Goldmann, M.D., (610/397-2383).

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

q/mcs/ltr/456
Attachment

Federal Express #1
Desk copy w/attachments (8): Ms. Robin Anderson, HFD-540, Rm. N-248 Federal Express #1

DUPLICATE
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Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

May 13, 1997

NEW CORRESPONDENCE

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MERCK
Research Laboratories

Jonathan Wilkin, M.D., Director
Division of Dermatological Drug Products
HFD-540, Room N-214
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

NDA 20-788: PROPECIA™
(Finasteride)

Reference is made to the above New Drug Application (NDA) submitted on December 20, 1997; and a 90-Day Meeting held on March 19, 1997. During that meeting, Merck Research Laboratories (MRL) agreed to design and conduct a short-term study of the impact of the medicated shampoo used in the pivotal clinical studies on the hair count technology.

By this letter and attachment, MRL is providing a Draft Synopsis for the proposed study of the hair count technology. MRL is continuing to develop the complete protocol and anticipates a target date for beginning the study within the next four to six weeks. Therefore, I will contact Ms. Robin Anderson in the near future to confirm the Agency's acceptance of the basic outline of the study presented in the Draft Synopsis.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.

mcs/q/ltr/444.doc
Attachment
Federal Express #1

Desk Copies w/Attachment:
Ms. Robin Anderson, HFD-540, CRP2 N-248, Federal Express #1
Dr. Hon Sum Ko, HFD-540, CRP2 N-223, Federal Express #1

REVIEWS COMPLETED
CDD ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CDD INITIALS DATE

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

ORIGINAL

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

NC

April 29, 1997

MERCK
Research Laboratories

Robin Anderson, Project Manager
Division of Dermatological Drug Products
HFD-540, Room N-428
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

Dear Ms. Anderson:

NDA 20-788: PROPECIA™

Reference is made to the application cited above and to a telephone conversation on April 18, 1997 between you and myself in which you requested 2 extra copies of the Safety Update Report submitted on April 18, 1997.

Enclosed, as requested, are two (2) copies of the Safety Update Report.

Please direct questions or need for additional information to Robert E. Silverman, M.D., Ph.D. (610/397-2944). or, in my absence Bonnie J. Goldmann M.D. (610/397-2383).

Sincerely

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Attachments:

Federal Express

Q/young/sarfert/788.doc

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

ORIGINAL

MERCK
Research Laboratories

April 24, 1997

Jonathan Wilkin, M.D., Director
Division of Dermatological Drug Products
HFD-540, Room N-214
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

NC
NEW CORRESP

NDA 20-788: PROPECIA™
(Finasteride)

Reference is made to the above New Drug Application and a 90-Day Meeting between the Agency and Merck Research Laboratories (MRL) on March 19, 1997.

By copy of this letter and attachment, MRL is providing its minutes of the March 19 meeting. We would request a copy of the Agency's minutes when they become available. MRL anticipates further discussion with the Agency in the near future on the outstanding issues from the meeting including additional data related to the impact of medicated shampoo on hair count methodology, additional data from ongoing long term studies, the trademark and the scheduling of an Advisory Committee meeting.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

q/mcs/nn/438

Sincerely,

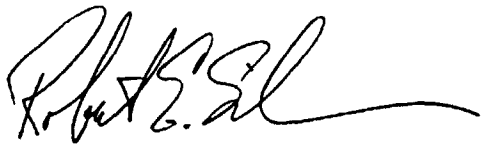
Robert E. Silverman, M.D., Ph.D.

Attachment
Federal Express #1
Desk Copy: (w/att.) Robin Anderson, Project Manager, HFD-540, CRP2 N248,
Federal Express #1

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,



Robert E. Silverman, M.D., Ph.D.

mcs/q/ltr/439

Federal Express #1

Desk Copies: Ms. Robin Anderson, HFD-540, CRP2 N248, Federal Express #1 (via Fax)
Dr. Valerie Freidlin, HFD-540 CRP2 N250, Federal Express #1
Dr. Hon Ko, HFD-540, CRP2 N223, Federal Express #1